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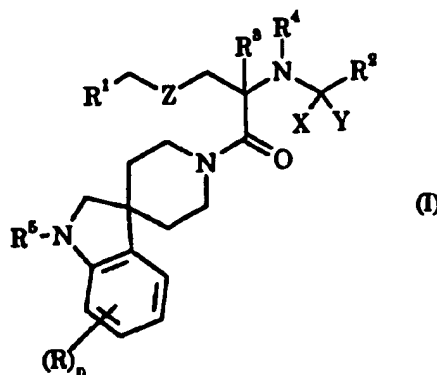
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(54) Title: SPIRO-SUBSTITUTED AZACYCLIC DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

The present invention relates to compounds of formula (I), wherein n is zero, 1, 2 or 3; R represents C₁-alkyl, C₁-alkoxy, hydroxy, halogen, cyano, trifluoromethyl, SO₂C₁-alkyl, NR^aR^b, NR^aCOR^b or CONR^aR^b, where R^a and R^b are each H, C₁-alkyl, phenyl or trifluoromethyl; R¹ represents phenyl optionally substituted by 1, 2 or 3 of C₁-alkyl, C₂-alkenyl, C₂-alkynyl, C₃-7cycloalkyl, C₃-7cycloalkylC₁-alkyl, -O(CH₂)_pO- (where p is 1 or 2), halogen, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b; naphthyl; benzhydryl; or benzyl, where the naphthyl group or each phenyl moiety of benzyl and benzhydryl may be substituted by C₁-alkyl, C₁-alkoxy, halogen or trifluoromethyl; R² represents hydrogen, a substituent as defined for R¹ or heteroaryl selected from indazolyl, thienyl, furanyl, pyridyl, thiazolyl, tetrazolyl and quinolinyl; wherein each heteroaryl may be substituted by C₁-alkyl, C₁-alkoxy, halogen or trifluoromethyl; R³ and R⁴ are each H or C₁-alkyl or R³ and R⁴ together are linked so as to form a C₁-3alkylene chain; R⁵ represents H, C₁-alkyl, C₃-7cycloalkyl, C₃-7cycloalkylC₁-alkyl, phenylC₁-alkyl, CO₂R^a, CONR^aR^b, SOR^a or SO₂R^a, wherein the phenyl moiety may be substituted by C₁-alkyl, C₁-alkoxy, halogen or trifluoromethyl; X and Y are each H, or together represent =O; and Z represents a bond, O, S, SO, SO₂, NR⁶, or -(CR⁶R⁶)- where R⁶ is H or C₁-alkyl; or a pharmaceutically acceptable salt thereof. The compounds are of particular use in the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia.



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SPIRO-SUBSTITUTED AZACYCLIC DERIVATIVES
AND THEIR USE AS THERAPEUTIC AGENTS

5 This invention relates to a class of spiro-substituted azacyclic compounds, which are useful as tachykinin antagonists. More particularly, the compounds of the invention comprise an azacyclic ring system spiro-substituted by an indolyl moiety and a substituted serine derived moiety.

10 The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

 The tachykinins are distinguished by a conserved carboxyl-terminal sequence:



15 At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P,
20 NKA and NKB as the NK₁, NK₂ and NK₃ receptors, respectively.

 Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory
25 diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including
30 cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R.

Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

For instance, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem.*, (1982) 25, 1009) and in arthritis [Levine *et al* in *Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al* in *Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al*, *Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al*, *Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al*, *Science* (1988) 241, 1218-21 and Kimball *et al*, *J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al*, *PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner *et al*, *Science* (1990) 250,

279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC)

5 [Langdon *et al*, *Cancer Research* (1992) 52, 4554-7].

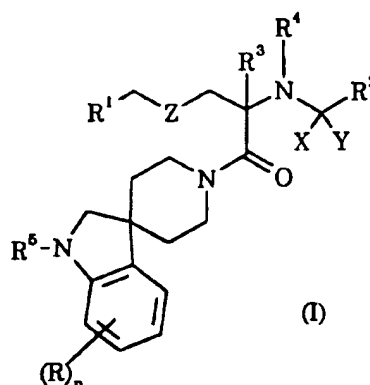
Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod *et al*, poster C.I.N.P. XVIIIth Congress, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia
10 (*Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynaud's disease, fibrosing and
15 collagen diseases such as scleroderma and eosinophilic fasciitis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythematosus (European patent specification no. 0 436
20 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

In view of their metabolic instability, peptide derivatives are likely
25 to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin antagonists are sought.

In essence, this invention provides a class of potent non-peptide tachykinin antagonists.

The present invention provides a compound of formula (I), or a
30 pharmaceutically acceptable salt thereof.



wherein

n is zero, 1, 2 or 3;

R represents C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, halogen, cyano,
 5 trifluoromethyl, SO₂C₁₋₆alkyl, NR^aR^b, NR^aCOR^b, or CONR^aR^b, where R^a
 and R^b each independently represent hydrogen, C₁₋₆alkyl, phenyl or
 trifluoromethyl;

R¹ represents unsubstituted phenyl or phenyl substituted by 1, 2 or
 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl,
 10 C₃₋₇cycloalkylC₁₋₄alkyl, -O(CH₂)_pO- where p is 1 or 2, halogen, cyano, nitro,
 trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a, NR^aR^b, NR^aCOR^b,
 NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b, where R^a and R^b are as previously
 defined; naphthyl; benzhydryl; or benzyl, where the naphthyl group or
 each phenyl moiety of benzyl and benzhydryl may be substituted by
 15 C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl;

R² represents hydrogen; unsubstituted phenyl or phenyl substituted
 by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,
 C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, -O(CH₂)_pO- where p is 1 or 2,
 halogen, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a,
 20 SO₂R^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b, where R^a
 and R^b are as previously defined; heteroaryl selected from indazolyl,
 thienyl, furanyl, pyridyl, thiazolyl, tetrazolyl and quinolinyl; naphthyl;
 benzhydryl; or benzyl; wherein each heteroaryl, the naphthyl group and
 each phenyl moiety of benzyl and benzhydryl may be substituted by
 25 C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl;

R³ and R⁴ each independently represents hydrogen or C₁₋₆alkyl or R³ and R⁴ together are linked so as to form a C₁₋₃alkylene chain;

R⁵ represents hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenylC₁₋₄alkyl, CO₂R^a, CONR^aR^b, SOR^a or SO₂R^a,
5 wherein the phenyl moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl, and R^a and R^b are as previously defined;

X and Y each independently represents hydrogen, or together form a group =O; and

Z represents a bond, O, S, SO, SO₂, NR⁶, or -(CR⁶R⁶)- where each R⁶
10 is hydrogen or C₁₋₆alkyl.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to
15 the formulae herein may represent straight or branched groups. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl and n-, sec-, iso- or tert-butyl. The cycloalkyl groups referred to above may be, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Similarly, suitable cycloalkylalkyl groups include cyclopropylmethyl. Suitable
20 alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine and fluorine.

The present invention includes within its scope prodrugs of the
25 compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I).

Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs",
30 ed. H. Bundgaard, Elsevier, 1985.

Those compounds according to the invention which contain one or more chiral centres may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

5 Preferably n is zero.

 Preferably R^1 represents unsubstituted phenyl or phenyl substituted by one or two groups selected from C_{1-6} alkyl such as methyl, halogen such as chlorine, fluorine and bromine, and trifluoromethyl. Particularly preferred substituents are chlorine and trifluoromethyl.

10 Most preferably, R^1 represents disubstituted phenyl, in particular 3,4-disubstituted phenyl, especially 3,4-dichlorophenyl.

 Suitable values for the group R^2 include unsubstituted or substituted phenyl, 5-membered heteroaryl such as thienyl or furanyl, 6-membered heteroaryl such as pyridyl, quinolinyl, naphthyl, and
15 benzhydryl.

 Preferably R^2 represents unsubstituted or substituted phenyl, especially unsubstituted phenyl.

 When R^2 represents substituted phenyl it preferably represents dichlorophenyl, especially 3,4-dichlorophenyl.

20 Preferably R^3 and R^4 each independently represent hydrogen.

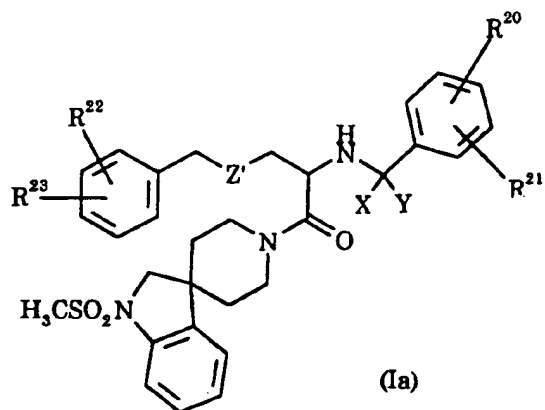
 Preferably R^5 represents the group SO_2R^* where R^* is as previously defined. Particularly preferred is the group $SO_2(C_{1-6}alkyl)$, especially SO_2CH_3 .

 Preferably X and Y are both hydrogen atoms.

25 Preferably Z is an oxygen atom.

 In another preferred class of compounds of formula (I), Z is preferably $-CH_2-$.

 A particular sub-class of compounds according to the invention is represented by compounds of formula (Ia), and pharmaceutically
30 acceptable salts thereof:



wherein

X and Y are as defined for formula (I);

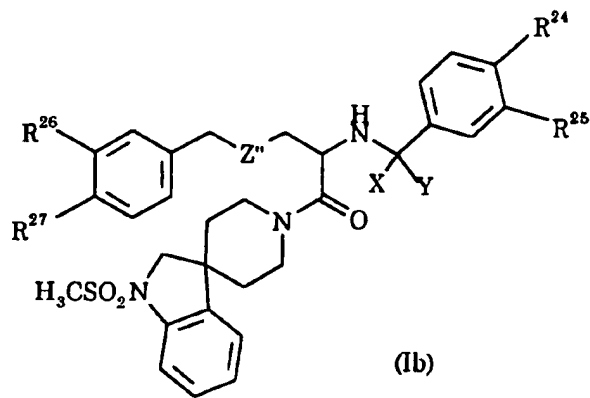
5 Z' is O, S or $-\text{CH}_2-$, especially O or S;

R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, halogen, trifluoromethyl, OR^a , or NR^aR^b , where R^a and R^b are as previously defined; and

10 R^{22} and R^{23} independently represent hydrogen or halogen, preferably hydrogen or chlorine.

Particular values of R^{20} and R^{21} include hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy and dimethylamino.

Another preferred sub-class of compounds according to the invention is represented by compounds of formula (Ib), and
15 pharmaceutically acceptable salts thereof:



wherein

Z" is O or -CH₂-, especially O;

R²⁴ and R²⁵ independently represent hydrogen or chlorine; and

5 R²⁶ and R²⁷ independently represent hydrogen or chlorine, with the proviso that at least one of R²⁶ and R²⁷ represents chlorine.

Specific compounds within the scope of the present invention include:

- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-pyridylcarboxamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzamido)propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-chlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzamido)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,5-dichlorobenzamido)propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzamido)propionamide;
- 30 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzamido)propionamide;

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-benzamidopropionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-(2-propyloxy)benzamido)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(1-naphthyl)carboxamido]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(2-naphthyl)carboxamido]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(phenylacetamido)propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorophenylacetamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(3,5-bis(trifluoromethyl)phenyl)acetamido]propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(diphenylacetamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylcarboxamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylcarboxamido)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(8-quinolinylcarboxamido)propionamide;
- and pharmaceutically acceptable salts thereof.

Particularly preferred compounds within the scope of the present invention include:

- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-methoxybenzylamino)propionamide;
- 30 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-benzyloxypropionamide;

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzylamino)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-chlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-bromobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-fluorobenzylamino)propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-cyanobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-nitrobenzylamino)propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methylbenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methoxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-methoxybenzylamino)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-(dimethylamino)benzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzylamino)propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzylamino)propionamide;
- 30

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dimethoxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chloro-5-methoxybenzylamino)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-methylenedioxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(1-naphthylmethylamino)propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-naphthylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylmethylamino)propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-pyridylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-furylmethylamino)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(5-methylfur-2-yl)methylamino]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(3-methylthiophen-2-yl)methylamino]propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(5-methylthiophen-2-yl)methylamino]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(N-(3,4-dichlorobenzyl)-N-(methyl)amino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(2-chlorobenzyloxy)propionamide;
- 30

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(3-chlorobenzoyloxy)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(4-chlorobenzoyloxy)propionamide;
5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(2-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(4-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(benzylthio)-2-(3,4-dichlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(3,4-dichlorobenzoyloxy)propionamide;
15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
and pharmaceutically acceptable salts thereof.

Further preferred compounds of the present invention include:

- N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naph-2-yl)methoxy]propionamide;
20 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naph-1-yl)methoxy]propionamide;
N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-[N-(methyl)benzylamino]-3-(3,4-dichlorobenzoyloxy)propionamide;
25 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzoyloxy)-2-(dimethyl)aminopropionamide;
N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylthio)-2-(benzylamino)propionamide;
N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylsulfonyl)-2-(benzylamino)propionamide;
30

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2,3-bis(benzylamino)propionamide;

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzylamino)propionamide;

5 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionamide;

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-phenylpentanamide;

10 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)pentanamide;

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)butanamide;

and pharmaceutically acceptable salts thereof.

Especially preferred compounds of the present invention include:

15 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzoyloxy)propionamide;

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(3,4-dichlorobenzylamino)-3-(3,4-dichlorobenzoyloxy)propionamide;

and pharmaceutically acceptable salts thereof.

20 For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention (such as the dibenzoyltartrate salts) or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this

25 invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or

30 p-toluenesulphonic acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a

suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

Preferred salts of the compounds according to the invention include the hydrochloride and p-toluenesulphonic acid salts.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage

forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be

appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infontrol™, Lipofundin™
5 and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water.
10 It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5
15 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and
20 suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably
25 sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally
30 or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

5 The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative
10 disorders such as dementia, including AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example
15 AIDS related neuropathy, diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; neuronal damage, such as cerebral ischemic damage and cerebral edema in cerebrovascular disorders; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such
20 as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, asthma, and bronchospasm; airways diseases modulated by neurogenic inflammation; diseases characterised by neurogenic mucus secretion, such as cystic fibrosis; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome,
25 hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, and amyloidosis; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, ocular inflammation, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as
30 conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; ophthalmic conditions associated with cell proliferation such as

proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders including the withdrawal response produced by chronic treatment with, or abuse of, drugs such as benzodiazepines, opiates, cocaine, alcohol and nicotine; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed, post-operative, late phase or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, surgery, migraine, opioid analgesics, and variations in intracranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

Hence, the compounds of the present invention may be of use in the treatment of physiological disorders associated with excessive stimulation of tachykinin receptors, especially neurokinin-1 receptors, and as neurokinin-1 antagonists for the control and/or treatment of any of the aforementioned clinical conditions in mammals, including humans.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the
5 treatment of emesis, including acute, delayed, post-operative, late phase or anticipatory emesis, such as emesis or nausea induced by chemotherapy, radiation, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, mechanical stimulation, gastrointestinal obstruction, reduced
10 gastrointestinal motility, visceral pain, psychological stress or disturbance, high altitude, weightlessness, opioid analgesics, intoxication, resulting for example from consumption of alcohol, surgery, migraine, and variations in intracranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents
15 including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic
20 acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *"Nausea and Vomiting: Recent Research and
25 Clinical Advances"*, Eds. J. Kuucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin
30 (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin

and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or GABA_B receptor agonists such as baclofen. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, triamcinolone, triamcinolone acetonide, flunisolide, budesonide, or others such as those disclosed in US patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. Dexamethasone (Decadron™) is particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other
5 neuralgias, asthma, osteoarthritis, rheumatoid arthritis, headache and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention
10 provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of
15 tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to
20 employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2
25 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such as a compound selected from those disclosed in European patent
30 specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the

treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method
5 comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically
10 acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists, especially sumatriptan.

15 Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present
20 invention may be used in conjunction with an antiinflammatory agent such as a bradykinin receptor antagonist.

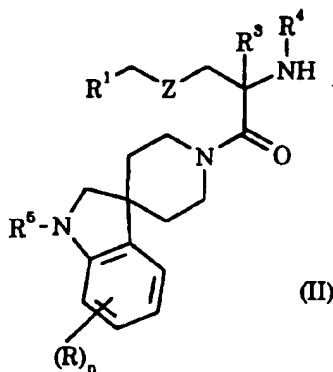
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about
25 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be
30 administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to process (A), compounds of formula (I) wherein X and Y are both hydrogen, may be prepared from compounds of formula (II):



wherein R, R^1 , R^3 , R^4 , R^5 , Z and n are as defined for formula (I), by reaction with an aldehyde of formula R^2-CHO in the presence of a reducing agent.

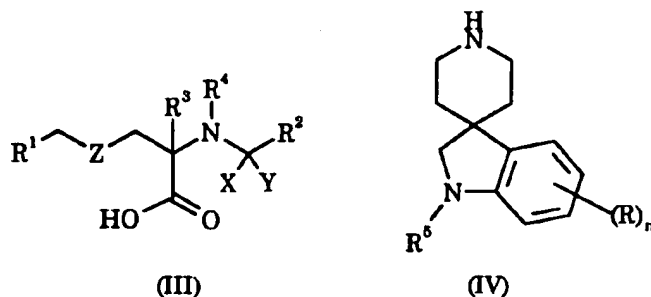
Suitable reducing agents of use in the reaction include hydride reducing agents such as sodium cyanoborohydride or sodium borohydride.

The reaction is conveniently effected in a suitable solvent such as dimethylformamide or dichloromethane, conveniently at room temperature.

According to a process (B), compounds of formula (I) wherein X and Y together form a group =O, may be prepared by the reaction of a compound of formula (II) with an acyl halide of formula $R^2\text{-COHal}$ where Hal is a halogen atom, typically chlorine, fluorine or bromine, especially chlorine.

The reaction is conveniently effected in the presence of an acylation catalyst such as 4-dimethylaminopyridine in a suitable solvent such as dichloromethane at a temperature between -10°C and 40°C , conveniently at room temperature.

According to a further process (C), compounds of formula (I) may be prepared by the reaction of a compound of formula (III) with a piperidinyl derivative of formula (IV):



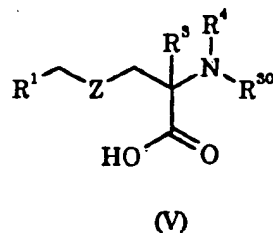
wherein R, R^1 , R^2 , R^3 , R^4 , R^5 , X, Y, Z and n are as defined for formula (I) with the proviso that R^5 is not hydrogen.

The reaction is effected in the presence of a suitable coupling agent, such as dicyclocarbonyldiimide, N,N'-carbonyldiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide optionally in the presence of an additive such as 1-hydroxybenzotriazole.

The reaction is conveniently effected in a suitable solvent such as dimethylformamide, conveniently at room temperature.

Further useful synthetic methods are those commonly used in standard syntheses of amino acids, for example, as described in *Chemistry and Biochemistry of the Amino Acids*, Ed. G. C. Barrett, Chapman and Hall, London 1985.

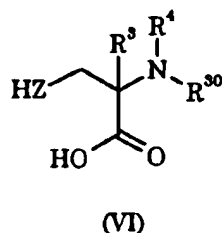
Compounds of formula (II) may be prepared from a suitably protected compound of formula (V):



5 wherein R¹, R³, R⁴, and Z are as defined for formula (I) and R³⁰ is an amine protecting group, for example, *tert*-butoxycarbonyl (*t*-BOC), by reaction with a compound of formula (IV) using the conditions of process (C), followed by deprotection in a conventional manner, for instance using hydrogen chloride in methanol.

10 Compounds of formula (III) may be prepared from a deprotected derivative corresponding to a compound of formula (V) by reaction with an aldehyde of formula R²-CHO under the conditions of process (A) or an acyl halide of formula R²-COHal under the conditions of process (B).

15 Compounds of formula (V) may be prepared by reaction of a compound of formula (VI):



wherein R³, R⁴, and Z are as defined for formula (I) and R³⁰ is a protecting group as defined above, by reaction with compound of the formula

20 R¹-CH₂L, where L is a leaving group, for example, a halogen atom such as chlorine, bromine or iodine, or an alkyl- or arylsulphonyloxy group such as a mesylate or tosylate group. The reaction is effected in the presence of a suitable base, for example, an alkali metal hydride such as sodium hydride.

Compounds of formula (VI) are commercially available or may be prepared by known procedures.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds which contain one or more chiral centres may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of the invention were tested by the methods set out at pages 82 to 85 of International Patent Specification No. WO 93/04040. The compounds were found to be active with IC_{50} at the NK_1 receptor of less than 300nM.

The compounds of this invention may be formulated as specifically illustrated at pages 81 to 82 of International Patent Specification No. 93/04040.

The following Examples illustrate the preparation of compounds according to the invention.

DESCRIPTION 1

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(t-butoxycarbonylamino)propionamide

To N-*tert*-butoxycarbonyl-*O*-benzyl-*D,L*-serine (2.9g, 9.83mmol), and
5 1-hydroxybenzotriazole (278mg), was added dry dimethylformamide (30ml), and the mixture cooled to 4°C. 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.36g) was added, and the resulting mixture stirred for 1 hour at room temperature. The resulting solution was then cooled to -15°C and 1-methanesulfonylspiro(3H-indole-3,4'-piperidine)
10 hydrochloride (2.93g) was then added, followed after stirring for 5 minutes, by triethylamine (1.50ml). The resulting mixture was warmed to room temperature, stirred at room temperature for 1.5 hours, then diluted with ethyl acetate (150ml), washed with water (100ml), and saturated aqueous sodium hydrogen carbonate (50ml). The organic layer was dried
15 over sodium sulfate, filtered, and solvents evaporated at reduced pressure. The residue was subjected to chromatography on silica gel (eluent 5% methanol/dichloromethane) to afford the title compound as a colourless solid. m/e (Cl⁺) 544 (MH⁺). m.p. 53-56°C.

20

DESCRIPTION 2

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-amino-3-benzyloxypropionamide hydrochloride

To the product of Description 1 (0.48g, 1mmol), was added a saturated solution of hydrogen chloride in methanol (150ml). The
25 resulting solution was allowed to stand at room temperature for 24 hours. After evaporation of the volatiles at reduced pressure, the residue was dissolved in dichloromethane (50ml), then diluted with diethyl ether (150ml). Trituration of the mixture afforded the title compound as a colourless solid, recovered by filtration. Found: C, 56.65; H, 6.62; N, 8.45.
30 C₂₃H₂₉N₃O₄S.HCl.0.5(H₂O) requires: C, 56.48 H, 6.39; N, 8.59%. m/e (Cl⁺) 444 (MH⁺).

EXAMPLE 1

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzamido)propionamide

5 To the product of Description 2 (1.15g, 2.4mmol), dissolved in dry dichloromethane (5ml), stirred at 4°C, was added triethylamine (0.700ml), followed by 3,4-dichlorobenzoyl chloride (552mg), and 4-dimethylamino-pyridine (10mg). The resulting mixture was warmed to room temperature and then stirred for a further 3 hours. The reaction mixture was diluted
10 with ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (50ml). The organic layer was dried over sodium sulfate, filtered, and solvents evaporated at reduced pressure. The residue was subjected to chromatography on silica gel (eluent 5% methanol/dichloromethane) to afford the title compound as a colourless
15 foam. Found: C, 58.71; H, 5.06; N, 6.74. $C_{30}H_{31}N_3O_5SCl$ requires: C, 58.44 H, 5.07; N, 6.85%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 2

20 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzylamino)propionamide hydrochloride

a) N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-amino propionamide

25 The product of Description 2 was stirred vigorously with saturated aqueous sodium carbonate and ethyl acetate for 30 minutes. The organic layer was then separated, dried over sodium sulfate, filtered, and solvents evaporated at reduced pressure to afford the title compound.

b) N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzylamino)propionamide hydrochloride
30

To the product of step (a) (590mg, 1.33mmol), dissolved in dry dichloromethane (2.5ml), was added 3,4-dichlorobenzaldehyde (260mg), and anhydrous magnesium sulfate (1.3g). The resulting mixture was stirred for 18 hours, then diluted with dichloromethane (50ml), filtered, and the solvents evaporated at reduced pressure. The residue was dissolved in methanol (3ml) and sodium borohydride (55mg) added with stirring. The resulting mixture was stirred for 1 hour at room temperature, and the solvents evaporated at reduced pressure. The residue was partitioned between water (15ml) and ethyl acetate (25ml). The organic layer was separated, dried over sodium sulfate, filtered, and solvents evaporated at reduced pressure. The residue was subjected to chromatography on silica gel (eluent 2.5% methanol/dichloromethane) to afford a colourless foam. This was dissolved in ethyl acetate, and treated with a saturated solution of hydrogen chloride in ether. The title compound was isolated by filtration as a colourless solid. Found: C, 56.64; H, 5.25; N, 6.61. $C_{30}H_{33}N_3O_4SCl_2.HCl$ requires: C, 56.39 H, 5.36; N, 6.58%. m/e (Cl^+) 602 (MH^+).

EXAMPLE 3

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-pyridylcarboxamido)propionamide

To nicotinic acid (77mg), and 1-hydroxybenzotriazole (85mg), in dry dimethylformamide (2.5 ml), was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (120mg), and the resulting mixture stirred for 1 hour at room temperature. Triethylamine (0.087ml) was then added, followed by the product of Description 2 (300mg). The resulting mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate (50ml), washed with water (100ml), and saturated aqueous sodium hydrogen carbonate (25ml). The organic layer was dried over sodium sulfate, filtered, and solvents evaporated at reduced pressure. The residue was subjected to chromatography on silica gel (eluent ethyl

acetate) to afford the title compound as a colourless solid. m/e (Cl⁺) 549 (MH⁺). m.p. 80-83°C.

EXAMPLE 4

5 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-methoxybenzylamino)propionamide hydrochloride

To the product of Description 2 (0.48g, 1mmol), in dry dimethylformamide (1ml), was added 2-methoxybenzaldehyde (0.11g, 1.1mmol), followed by sodium cyanoborohydride (0.09g, 2 mmol), and the
10 mixture stirred at room temperature for 16 hours. The reaction was diluted with ethyl acetate (20ml), and washed with water (5 x 10ml), dried over magnesium sulfate, filtered, and the solvent evaporated at reduced pressure. The residue was purified by chromatography on silica gel, (eluent 1% methanol/dichloromethane), to afford the title compound.
15 Found: C, 61.84; H, 6.43; N, 6.68. C₃₁H₃₇N₃O₅S.HCl.0.25(H₂O) requires: C, 61.58; H, 6.42; N, 6.95%. m/e (Cl⁺) 564 (MH⁺).

By the method of Example 2, or Example 4, the following compounds were prepared from the known aldehydes.

20

EXAMPLE 5

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-benzyloxypropionamide hydrochloride

Found: C, 61.47; H, 6.31; N, 7.62. C₃₀H₃₅N₃O₄S.HCl.H₂O requires: C, 61.47; H, 6.31; N, 7.62%.

25

EXAMPLE 6

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzylamino)propionamide hydrochloride

Found: C, 58.90; H, 5.80; N, 6.69. C₃₀H₃₄N₃O₄SCl.HCl.0.25(H₂O) requires: C, 59.16; H, 5.88; N, 6.90%. m/e (Cl⁺) 568 (MH⁺).

30

EXAMPLE 7

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzylamino)propionamide hydrochloride

5 Found: C, 58.23; H, 5.78; N, 6.63. $C_{30}H_{34}N_3O_4SCl.HCl.H_2O$ requires: C, 57.87; H, 5.99; N, 6.74%. m/e (Cl^+) 568 (MH^+).

EXAMPLE 8

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-chlorobenzylamino)propionamide hydrochloride

10 Found: C, 58.59; H, 5.93; N, 6.76. $C_{30}H_{34}N_3O_4SCl.HCl.0.5(H_2O)$ requires: C, 58.72; H, 5.91; N, 6.85%. m/e (Cl^+) 568 (MH^+).

EXAMPLE 9

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-bromobenzylamino)propionamide hydrochloride

15 Found: C, 54.08; H, 5.57; N, 6.16. $C_{30}H_{34}N_3O_4SBrHCl.H_2O$ requires: C, 54.01; H, 5.59; N, 6.29%. m/e (Cl^+) 614 (MH^+).

EXAMPLE 10

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-fluorobenzylamino)propionamide hydrochloride

20 Found: C, 60.24; H, 5.94; N, 6.76. $C_{30}H_{34}N_3O_4SF.HCl.0.5(H_2O)$ requires: C, 60.34; H, 6.08; N, 7.04%. m/e (Cl^+) 552 (MH^+).

EXAMPLE 11

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-cyanobenzylamino)propionamide hydrochloride

25
30 Found: C, 60.42; H, 5.78; N, 8.81. $C_{31}H_{34}N_4O_4S.HCl.H_2O$ requires: C, 60.72; H, 6.08; N, 9.13%. m/e (Cl^+) 559 (MH^+).

EXAMPLE 12

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-nitrobenzylamino)propionamide hydrochloride

Found: C, 56.99; H, 5.64; N, 8.64. $C_{30}H_{34}N_4O_6S \cdot HCl \cdot H_2O$ requires: C, 56.91; H, 5.84; N, 8.85%. m/e (Cl^+) 579 (MH^+).

EXAMPLE 13

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methylbenzylamino)propionamide hydrochloride

Found: C, 61.79; H, 6.64; N, 6.83. $C_{31}H_{37}N_3O_4S \cdot HCl \cdot H_2O$ requires: C, 61.83; H, 6.69; N, 6.97%. m/e (Cl^+) 548 (MH^+).

EXAMPLE 14

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methoxybenzylamino)propionamide hydrochloride

Found: C, 60.06; H, 6.32; N, 6.41. $C_{31}H_{37}N_3O_5S \cdot HCl \cdot H_2O$ requires: C, 60.23; H, 6.52; N, 6.79%. m/e (Cl^+) 564 (MH^+).

EXAMPLE 15

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-methoxybenzylamino)propionamide hydrochloride

Found: C, 58.89; H, 6.40; N, 6.94. $C_{31}H_{37}N_3O_5S \cdot HCl \cdot 2(H_2O)$ requires: C, 58.53; H, 6.65; N, 6.61%. m/e (Cl^+) 564 (MH^+).

EXAMPLE 16

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-(dimethylamino)-benzylamino)propionamide hydrochloride

Found: C, 57.67; H, 6.42; N, 7.96. $C_{32}H_{40}N_4O_4S \cdot 2(HCl) \cdot (H_2O)$ requires: C, 57.56; H, 6.64; N, 8.39%. m/e (Cl^+) 577 (MH^+).

EXAMPLE 17

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzylamino)propionamide hydrochloride

Found: C, 55.20; H, 5.58; N, 6.14. $C_{30}H_{33}N_3O_4SCl_2.HCl.0.5(H_2O)$ requires:
5 C, 55.60; H, 5.44; N, 6.48%. m/e (Cl^+) 602 (MH^+).

EXAMPLE 18

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzylamino)propionamide hydrochloride

10 Found: C, 54.96; H, 5.47; N, 6.45. $C_{30}H_{33}N_3O_4SCl_2.HCl.H_2O$ requires: C, 54.84; H, 5.53; N, 6.40%. m/e (Cl^+) 602 (MH^+).

EXAMPLE 19

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzylamino)propionamide hydrochloride

15 Found: C, 54.48; H, 5.13; N, 6.36. $C_{30}H_{33}N_3O_4SCl_2.HCl.H_2O$ requires: C, 54.84; H, 5.53; N, 6.40%. m/e (Cl^+) 602 (MH^+).

EXAMPLE 20

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzylamino)propionamide hydrochloride

20 m/e (Cl^+) 602 (MH^+).

EXAMPLE 21

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dimethoxybenzylamino)propionamide hydrochloride

25 Found: C, 59.83; H, 6.40; N, 6.62. $C_{32}H_{39}N_3O_6S.HCl.0.5(H_2O)$ requires: C, 60.13; H, 6.47; N, 6.57%. m/e (Cl^+) 594 (MH^+).

EXAMPLE 22

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chloro-5-methoxybenzylamino)propionamide hydrochloride

Found: C, 57.22; H, 5.88; N, 6.35. $C_{31}H_{36}N_3O_6S.Cl.HCl.H_2O$ requires: C, 56.96; H, 6.16; N, 6.42%. m/e (Cl^+) 598 (MH^+).

EXAMPLE 23

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzylamino)propionamide hydrochloride

Found: C, 60.12; H, 6.68; N, 6.52. $C_{32}H_{39}N_3O_6S.HCl.0.5(H_2O)$ requires: C, 60.13; H, 6.47; N, 6.57%. m/e (Cl^+) 594 (MH^+).

EXAMPLE 24

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-methylenedioxybenzylamino)propionamide hydrochloride

Found: C, 59.98; H, 6.01; N, 6.64. $C_{31}H_{35}N_3O_6S.HCl.0.25(H_2O)$ requires: C, 60.18; H, 5.95; N, 6.79%. m/e (Cl^+) 578 (MH^+).

EXAMPLE 25

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(1-naphthylmethylamino)propionamide hydrochloride

Found: C, 64.71; H, 6.25; N, 6.58. $C_{34}H_{37}N_3O_4S.HCl.0.5(H_2O)$ requires: C, 64.90; H, 6.24; N, 6.67%. m/e (Cl^+) 584 (MH^+).

EXAMPLE 26

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-naphthylmethylamino)propionamide hydrochloride

Found: C, 63.72; H, 5.99; N, 6.51. $C_{34}H_{37}N_3O_4S.HCl.H_2O$ requires: C, 63.98; H, 6.31; N, 6.58%. m/e (Cl^+) 584 (MH^+).

EXAMPLE 27

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylmethylamino)propionamide dihydrochloride

Found: C, 56.88; H, 6.22; N, 9.42. $C_{29}H_{34}N_4O_4S \cdot 2(HCl) \cdot 0.5(H_2O)$ requires:
5 C, 56.91; H, 6.01; N, 9.15%. m/e (Cl^+) 535 (MH^+). mp = 98°C

EXAMPLE 28

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-pyridylmethylamino)propionamide dihydrochloride

10 m/e (Cl^+) 535 (MH^+). mp = 156-158°C

EXAMPLE 29

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylmethylamino)propionamide dihydrochloride

15 m/e (Cl^+) 535 (MH^+). mp = 135-137°C

EXAMPLE 30

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-furylmethylamino)propionamide dihydrochloride

20 m/e (Cl^+) 524 (MH^+). mp = 112°C

EXAMPLE 31

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(5-methylfur-2-yl)methylamino]propionamide hydrochloride

25 Found: C, 58.66; H, 6.78; N, 7.29. $C_{29}H_{35}N_3O_5S \cdot HCl \cdot H_2O$ requires: C, 58.82; H, 6.47; N, 7.09%. m/e (Cl^+) 537 (MH^+).

EXAMPLE 32

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-
[(3-methylthiophen-2-yl)methylamino]propionamide hydrochloride

Found: C, 57.85; H, 6.30; N, 6.64. $C_{29}H_{35}N_3O_4S_2.HCl.1.5(H_2O)$ requires: C,
5 57.79; H, 6.10; N, 6.97%. m/e (Cl^+) 554 (MH^+).

EXAMPLE 33

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-
[(5-methylthiophen-2-yl)methylamino]propionamide hydrochloride

10 Found: C, 55.70; H, 6.15; N, 6.40. $C_{29}H_{35}N_3O_4S_2.HCl.2(H_2O)$ requires: C,
55.62; H, 6.43; N, 6.71%. m/e (Cl^+) 554 (MH^+).

EXAMPLE 34

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-
15 (N-(3,4-dichlorobenzyl)-N-(methylamino)propionamide hydrochloride

To the product of Example 2 (113mg, 0.188mmol), suspended in dry
dimethylformamide (2ml), was added sodium cyanoborohydride (44mg),
paraformaldehyde (100mg), and the mixture was stirred at room
temperature for 16 hours. The reaction was diluted with ethyl acetate
20 (20ml), and washed with water (5 x 10ml), dried over magnesium sulfate,
filtered, and the solvent evaporated at reduced pressure. The residue was
purified by chromatography on silica gel, (eluent 2.5% methanol/
dichloromethane), to afford the title compound. Found: C, 56.05; H, 5.77;
N, 6.35. $C_{31}H_{35}N_3O_4S_2Cl_2.HCl.0.5(H_2O)$ requires: C, 56.24; H, 5.63; N,
25 6.35%. m/e (Cl^+) 616 (MH^+).

By the method of Example 1 the following compounds were
prepared from the known acid chlorides and the product of Description 2:

EXAMPLE 35

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzamido)propionamide

Found: C, 62.27; H, 5.79; N, 6.91. $C_{30}H_{32}N_3O_5SCl$ requires: C, 61.90; H, 5.54; N, 7.22%. m/e (Cl^+) 582 (MH^+).

EXAMPLE 36

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzamido)propionamide

Found: C, 61.78; H, 5.54; N, 6.96. $C_{30}H_{32}N_3O_5SCl$ requires: C, 61.90; H, 5.54; N, 7.22%. m/e (Cl^+) 582 (MH^+).

EXAMPLE 37

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-chlorobenzamido)propionamide

Found: C, 61.10; H, 5.49; N, 6.86. $C_{30}H_{32}N_3O_5SCl \cdot 0.5(H_2O)$ requires: C, 60.95; H, 5.63; N, 7.11%. m/e (Cl^+) 582 (MH^+).

EXAMPLE 38

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzamido)propionamide

Found: C, 56.51; H, 4.80; N, 6.34. $C_{30}H_{31}N_3O_5SCl_2 \cdot H_2O$ requires: C, 56.78; H, 5.24; N, 6.62%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 39

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzamido)propionamide

Found: C, 58.34; H, 4.73; N, 6.64. $C_{30}H_{31}N_3O_5SCl_2$ requires: C, 58.44; H, 5.06; N, 6.81%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 40

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,5-dichlorobenzamido)propionamide

Found: C, 56.80; H, 4.94; N, 6.53. $C_{30}H_{31}N_3O_5SCl_2 \cdot H_2O$ requires: C, 56.78;
5 H, 5.24; N, 6.62%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 41

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzamido)propionamide

10 Found: C, 57.67; H, 4.86; N, 6.30. $C_{30}H_{32}N_3O_5SCl_2 \cdot 0.6(H_2O)$ requires: C, 57.43; H, 5.17; N, 6.70%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 42

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzamido)propionamide

15 Found: C, 58.22; H, 4.86; N, 6.69. $C_{30}H_{31}N_3O_5SCl_2$ requires: C, 58.44; H, 5.06; N, 6.81%. m/e (Cl^+) 616 (MH^+).

EXAMPLE 43

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzamido)propionamide

20 Found: C, 59.50; H, 6.17; N, 6.35. $C_{32}H_{37}N_3O_7S \cdot 2(H_2O)$ requires: C, 59.70; H, 6.42; N, 6.53%. m/e (Cl^+) 608 (MH^+).

EXAMPLE 44

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-benzamidopropionamide

25 Found: C, 65.69; H, 5.84 N, 7.56. $C_{30}H_{33}N_3O_5S$ requires: C, 65.79; H, 6.07; N, 7.67%. m/e (Cl^+) 547 (MH^+). mp = 78-81°C.

EXAMPLE 45

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-(2-propyloxy)benzamido)propionamide

- 5 Found: C, 64.42; H, 6.20; N, 6.76. $C_{33}H_{39}N_3O_6S$ requires: C, 64.47; H, 6.56; N, 6.83%. m/e (Cl^+) 606 (MH^+).

EXAMPLE 46

- 10 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(1-naphthyl)carboxamidolpropionamide
m/e (Cl^+) 598 (MH^+).mp = 76-79°C.

EXAMPLE 47

- 15 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(2-naphthyl)carboxamidolpropionamide
m/e (Cl^+) 598 (MH^+).mp = 86-89°C.

EXAMPLE 48

- 20 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(phenylacetamido)propionamide
Found: C, 65.37; H, 6.03; N, 7.17. $C_{31}H_{35}N_3O_5S \cdot 0.5(H_2O)$ requires: C, 65.24; H, 6.34; N, 7.36%. m/e (Cl^+) 562 (MH^+).

EXAMPLE 49

- 25 N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-((3,4-dichlorophenyl)acetamido)propionamide
Found: C, 58.22; H, 5.19; N, 6.28. $C_{31}H_{33}N_3O_5SCl_2 \cdot 0.5(H_2O)$ requires: C, 58.21; H, 5.35; N, 6.57%. m/e (Cl^+) 630 (MH^+).

EXAMPLE 50

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(3,5-bis(trifluoromethyl)phenyl)acetamido]propionamide

Found: C, 56.86 H, 4.69; N, 5.92. $C_{33}H_{33}N_3O_5SF_6$ requires: C, 56.81; H, 4.77; N, 6.02%. m/e (Cl^+) 698 (MH^+).

EXAMPLE 51

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(diphenylacetamido)propionamide

Found: C, 69.10; H, 6.29; N, 6.25. $C_{37}H_{39}N_3O_5S \cdot 0.3(H_2O)$ requires: C, 69.09; H, 6.21; N, 6.53%. m/e (Cl^+) 638 (MH^+).

By the method of Example 3 the following compounds were prepared from the known acids and the product of Description 2:

EXAMPLE 52

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylcarboxamido)propionamide
m/e (Cl^+) 549 (MH^+). mp = 126-128°C.

EXAMPLE 53

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylcarboxamido)propionamidehydrochloride
m/e (Cl^+) 549 (MH^+). mp = 95-98°C.

EXAMPLE 54

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(8-quinolinylnylcarboxamido)propionamidehydrochloride
m/e (Cl^+) 599 (MH^+). mp = 80 - 83°C.

N-tert-butoxycarbonylserine was treated with sodium hydride and the appropriate substituted benzyl chlorides or bromides according to the

method of Sugano. H, and Miyoshi. M, *J. Org. Chem*, 41, 2352, (1976), to afford the corresponding N-tert-butoxycarbonyl-O-benzyl-serine after ester saponification. The following compounds were prepared from the N-tert-butoxycarbonyl-O-benzyl-serines according to the method of Descriptions 1 or 2, and Examples 1 or 2:

EXAMPLE 55

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(2-chlorobenzoyloxy)propionamide hydrochloride
Found: C, 57.83; H, 5.85; N, 6.30. $C_{30}H_{32}N_3O_4SCl.HCl.1.25(H_2O)$ requires: C, 57.64; H, 5.72; N, 6.72%. m/e (Cl^+) 568 (MH^+).

EXAMPLE 56

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3-chlorobenzoyloxy)propionamide hydrochloride
Found: C, 56.73; H, 5.89; N, 6.51. $C_{30}H_{32}N_3O_4SCl.HCl.2(H_2O)$ requires: C, 56.42; H, 5.84; N, 6.58%. m/e (Cl^+) 568 (MH^+).

EXAMPLE 57

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(4-chlorobenzoyloxy)propionamide hydrochloride
Found: C, 58.32; H, 5.81; N, 6.56. $C_{30}H_{32}N_3O_4SCl.HCl.H_2O$ requires: C, 58.06; H, 5.68; N, 6.77%. m/e (Cl^+) 568 (MH^+).

EXAMPLE 58

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(2-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide hydrochloride
Found: C, 52.74; H, 4.90; N, 5.96. $C_{30}H_{32}N_3O_4SCl_3.HCl.0.5(H_2O)$ requires: C, 52.79; H, 5.02; N, 6.18%. m/e (Cl^+) 636 (MH^+).

EXAMPLE 59

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide hydrochloride

Found: C, 52.33; H, 5.01; N, 5.75. $C_{30}H_{32}N_3O_4SCl_3 \cdot HCl \cdot H_2O$ requires: C, 52.10; H, 5.10; N, 6.07%. m/e (Cl^+) 636 (MH^+).

EXAMPLE 60

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(4-chlorobenzoyloxy)-2-(3,4-dichlorobenzylamino)propionamide hydrochloride

Found: C, 52.36; H, 4.77; N, 6.07. $C_{30}H_{32}N_3O_4SCl_3 \cdot HCl \cdot 0.5(H_2O)$ requires: C, 52.22; H, 4.89; N, 6.09%. m/e (Cl^+) 636 (MH^+).

EXAMPLE 61

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-[3,5-

bis(trifluoromethyl)benzoyloxy]-2-(3,5-dichlorobenzamido)-propionamide

Found: C, 50.99; H, 3.77; N, 5.60. $C_{32}H_{28}N_3O_5SCl_2F_6$ requires: C, 51.07; H, 3.88; N, 5.58%. m/e (Cl^+) 752 (MH^+).

The following compound was prepared from N-tert-butoxycarbonyl-S-benzyl-cysteine according to the method of Descriptions 1 and 2, and Example 2.

EXAMPLE 62

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(benzylthio)-2-(3,4-dichlorobenzylamino)propionamide hydrochloride

Found: C, 54.63; H, 5.11; N, 6.19. $C_{30}H_{33}N_3O_3S_2 \cdot HCl$ requires: C, 55.00; H, 5.23; N, 6.41%. m/e (Cl^+) 618 (MH^+). m.p. 215-217°C.

N-tert-Butoxycarbonylserine was treated with sodium hydride and the appropriate substituted benzyl or naphthylmethyl chlorides or bromides according to the method of Sugano, H. and Miyoshi, M., *J. Org. Chem.*, 41,

2352 (1976) to give, after ester saponification, the corresponding O-substituted N-*tert*-butoxycarbonylserine. The following compounds were prepared from the O-substituted N-*tert*-butoxycarbonylserines according to the method of Descriptions 1 or 2, and Examples 1 or 2:

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EXAMPLE 63

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naphth-2-yl)methoxy]propionamide, hydrochloride

Found: C, 64.64; H, 6.27; N, 6.34. $C_{34}H_{37}N_3O_4S.HCl.0.5H_2O$ requires: C, 64.90; H, 6.25; N, 6.68%. m/e (CI⁺) 584 (MH⁺).

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EXAMPLE 64

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naphth-1-yl)methoxy]propionamide, hydrochloride

Found: C, 63.64; H, 6.28; N, 6.59. $C_{34}H_{37}N_3O_4S.HCl.H_2O$ requires: C, 63.99; H, 6.32; N, 6.58%. m/e (CI⁺) 584 (MH⁺).

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EXAMPLE 65

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzoyloxy)propionamide, hydrochloride

Found: C, 55.53; H, 5.33; N, 6.85. $C_{30}H_{33}Cl_2N_3O_4S.HCl.0.5H_2O$ requires: C, 55.60; H, 5.44; N, 6.48%. m/e (CI⁺) 602 (MH⁺).

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EXAMPLE 66

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(3,4-dichlorobenzylamino)-3-(3,4-dichlorobenzoyloxy)propionamide, hydrochloride

Found: C, 49.64; H, 4.42; N, 5.47. $C_{30}H_{31}Cl_4N_3O_4S.HCl.H_2O$ requires: C, 49.64; H, 4.72; N, 5.79%. m/e (CI⁺) 670 (MH⁺).

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EXAMPLE 67

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-[N-(methyl)benzylamino]-3-(3,4-dichlorobenzoyloxy)propionamide, hydrochloride

5 Methyl iodide (0.1ml) was added to a mixture of N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzoyloxy)propionamide hydrochloride (48mg) and potassium carbonate (100mg) in dichloromethane/DMF (1:1, 4ml) and the mixture was stirred at room temperature for 16 hours. The mixture was diluted
10 with ether, washed with water (3 x), dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (3:1). The residue was dissolved in ethanolic hydrogen chloride and the solvent was evaporated under reduced pressure. The residue was triturated with
15 ether and the solid was collected and dried *in vacuo* to afford the title compound as a colourless solid. Found: C, 55.28; H, 5.68; N, 6.11. C₃₁H₃₅Cl₂N₅O₄S.HCl.H₂O requires: C, 55.48; H, 5.71; N, 6.26%. m/e (CI⁺) 616 (MH⁺).

EXAMPLE 68

20 N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzoyloxy)-2-(dimethyl)aminopropionamide, hydrochloride

a) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-amino-3-(3,4-dichlorobenzoyloxy)propionamide

25 N-*tert*-Butoxycarbonylserine was treated with sodium hydride and 3,4-dichlorobenzyl bromide according to the method of Sugano, H. and Miyoshi, M., *J. Org. Chem.*, 41, 2352 (1976) to give, after ester saponification, N-*tert*-butoxycarbonyl-O-(3,4-dichlorobenzyl)serine. This was then coupled according to the method of Description 1 and
30 deprotected according to the method of Description 2 to give the title compound. m/e (CI⁺) 512 (MH⁺).

b) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzyloxy)-2-(dimethyl)aminopropionamide, hydrochloride

Aqueous formaldehyde (38%, 1ml) and sodium cyanoborohydride (35mg) were added to a solution of the product of step (a) (240mg) in acetonitrile (20ml). Acetic acid was added until the reaction pH was 5 and the mixture was stirred at room temperature for 4 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and aqueous sodium hydroxide (1M). The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol (98:2). The residue was dissolved in ethanolic hydrogen chloride (5M, 3ml) and the solvent was evaporated under reduced pressure. The solid was recrystallized from isopropyl alcohol/ether to afford the title compound as a colourless solid (165mg, 61%). Found: C, 51.14; H, 5.70; N, 7.06. C₂₅H₃₁Cl₂N₃O₄S.HCl.0.5H₂O requires: C, 51.24; H, 5.68; N, 7.17%. m/e (CI⁺) 540 (MH⁺).

EXAMPLE 69

20 N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylthio)-2-(benzylamino)propionamide, hydrochloride

3,4-Dichlorobenzylmercaptan (0.3ml, 1.6mmol) was added dropwise to a stirred, cooled (0°C) suspension of sodium hydride (64mg, 1.6mmol) in DMF (5ml) and the mixture was stirred at 0°C for 1 hour. N-Benzyl-N-(benzyloxycarbonyl)serine-β-lactone [prepared according to Vederas, J. C., et. al., *J. Am. Chem. Soc.*, **109**, 4649 (1987), 0.40g, 1.2mmol] in DMF (5ml) was added and the mixture was warmed to 25°C and stirred for 2 hours [*J. Am. Chem. Soc.*, **107**, 7105 (1985)]. Ethyl acetate (50ml) and water (20ml) were added and the organic layer was washed with water (3 x 20ml), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (10ml) and

1-methanesulfonylspiro(3H-indole-3,4'-piperidine) hydrochloride (0.282g, 1.06mmol), triethylamine (0.31ml, 2.2mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.27g, 1.06mmol) were added. The mixture was stirred at room temperature for 2 hours, then ethyl acetate (50ml) and water (20ml) were added. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with ethyl acetate/hexane (30:70) to give *N*-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylthio)-2-[*N*-(benzyl)-benzyloxycarbonylamino]propionamide as a colourless oil (0.80g). A sample (0.10g) was dissolved in dichloromethane (3ml), cooled to -10°C and boron tribromide (1.0M in CH₂Cl₂, 0.7ml) was added. The mixture was warmed to 25°C for 20 minutes, aqueous sodium hydroxide (4M, 5ml) was added and the mixture was extracted with ethyl acetate (20ml). The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was treated with ethereal hydrogen chloride and the solid was collected and dried *in vacuo* to give the title compound as a colorless solid. NMR δ_H (360MHz, DMSO-d₆) 7.21-7.48 (10H, m), 7.03 (1H, m), 6.97 (1H, m), 4.05-4.21 (4H, m), 3.84-3.96 (2H, m), 3.64-3.73 (2H, m), 3.22 (1H, m), 2.99 (3H, s), 2.64-2.97 (4H, m), 1.67 (2H, m), 1.53 (2H, m). m/e (CI⁺) 618 (MH⁺).

EXAMPLE 70

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylsulfonyl)-2-(benzylamino)propionamide, hydrochloride
m-Chloroperoxybenzoic acid (2.6g, 8.8mmol) was added to *N*-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylthio)-2-[*N*-(benzyl)benzyloxycarbonylamino]propionamide (0.228g, 0.3mmol) in dichloromethane (2ml) and the mixture was stirred at room temperature for 16 hours. The mixture was diluted with dichloromethane (30ml) and washed with aqueous sodium bisulfite

(15ml), aqueous sodium carbonate (15ml) and brine (15ml). The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (1ml), cooled to -10°C and boron tribromide (1.0M in CH₂Cl₂, 0.7ml) was added. The mixture was warmed to 25°C for 20 minutes, aqueous sodium hydroxide (4M, 5ml) was added and the mixture was extracted with ethyl acetate (20ml). The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was treated with ethereal hydrogen chloride and the solid was collected and dried *in vacuo* to give the title compound as a colorless solid. NMR δ_H (360MHz, DMSO-d₆) 7.73 (2H, m), 7.46 (7H, m), 7.24-7.34 (2H, m), 7.09 (1H, m), 4.86 (1H, m), 4.78 (2H, s), 4.41 (1H, m), 4.04 (3H, m), 3.94 (2H, s), 3.81 (1H, m), 3.70 (1H, m), 3.24 (1H, m), 3.06 (3H, s), 2.85 (1H, m), 1.75 (4H, m). m/e (Cl⁺) 650 (MH⁺).

EXAMPLE 71

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2,3-bis(benzylamino)propionamide, hydrochloride

N-bis(trimethylsilyl)amine (0.11ml, 0.543mmol) was added to a solution of N-benzyl-N-(benzyloxycarbonyl)serine- β -lactone [prepared according to Vederas, J. C., et. al., *J. Am. Chem. Soc.*, **109**, 4649 (1987), 0.13 g, 0.418 mmol] in acetonitrile (2ml) and the mixture was stirred at room temperature for 16 hours [Vederas, J. C. et. al. *Tetrahedron Lett.*, **35**, 7605 (1994)]. The mixture was cooled to 0°C and aqueous hydrochloric acid (1M, 2ml) was added. The solvent was evaporated under reduced pressure and the residue was filtered. The filtrate was treated with aqueous sodium hydroxide (2M) until the pH was greater than 10 and di-*tert*-butyldicarbonate (200mg) was added. The mixture was stirred at room temperature for 12 hours, then ethyl acetate (50ml) and water (20ml) were added. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was

dissolved in dichloromethane (10ml) and 1-methanesulfonylspiro(3H-indole-3,4'-piperidine) hydrochloride (0.282g, 1.06mmol), triethylamine (0.31ml, 2.2mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.27g, 1.06mmol) were added. The mixture was stirred at room temperature for 2 hours, then ethyl acetate (50ml) and water (20ml) were added. The organic layer was separated and dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with ethyl acetate/hexane (30:70). The residue was dissolved in trifluoroacetic acid (2ml) and the mixture was stirred at room temperature for 5 minutes. The solvent was evaporated under reduced pressure and the residue was dissolved in ethanol. Palladium on carbon (0.4g) was added and the mixture was shaken under hydrogen (50 psi) for 16 hours. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with CH₂Cl₂/MeOH (98:2) and the residue was treated with ethereal hydrogen chloride. The solid was collected and dried *in vacuo* to give the title compound as a colourless solid, m.p. 158-160°C. m/e (Cl⁺) 533 (MH⁺).

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EXAMPLE 72

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzylamino)propionamide, dihydrochloride

a) Methyl 2-(tert-butoxycarbonylamino)-3-(3,4-dichlorobenzylamino)propionate

25

3,4-Dichlorobenzylamine (880mg) was added to a stirred solution of methyl 2-(tert-butoxycarbonylamino)acrylate (390mg) in methanol (30ml). The reaction mixture was warmed to reflux for 24 hours, cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by MPLC (70% ethyl acetate/n-hexane) to give the title compound as a clear oil (300mg). NMR δ_H (360MHz, CDCl₃) 1.45 (9H,

30

s), 2.95 (2H, d, J=3.5Hz), 3.70 (1H, d, J=14.0Hz), 3.75 (3H, s), 3.78 (1H, d, J=14.0Hz), 4.41 (1H, br s) 5.34 (1H, br s), 7.12 (1H, dd, J=7.0 and 1.0Hz), 7.37 (1H, d, J=7.0Hz), 7.41 (1H, d, J=1.0Hz).

5 b) Methyl 2-(tert-butoxycarbonylamino)-3-[N-(3,4-dichlorobenzyl)benzyloxycarbonylamino]propionate

Benzychloroformate (0.37ml) was added in a single portion to a stirred suspension of the product of step (a) (1.0g) in tetrahydrofuran/8% aqueous NaHCO₃ (50ml). After 2 hours the reaction was diluted with
10 water (50ml) and extracted with ethyl acetate (2x50ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a clear oil (1.09g). NMR δ_H (360MHz, CDCl₃) 1.43 (9H, s), 3.55-3.60 (2H, m), 3.70 (3H, s), 4.48 (2H, m), 5.21 (2H, m), 5.41 (1H, br s) 5.45 (1H, br s), 6.90-7.42 (8H,
15 m).

c) 2-(tert-Butoxycarbonylamino)-3-[N-(3,4-dichlorobenzyl)benzyloxycarbonylamino]propionic acid

Lithium hydroxide (62.4mg) was added to a solution of the product
20 of step (b) (1.0g) in tetrahydrofuran/water (30ml) . The resulting solution was stirred at room temperature for 4 hours, diluted with 1N HCl (50ml) and extracted with ethyl acetate (3x50ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a colourless foam (990 mg).
25 NMR δ_H (360MHz, CDCl₃) 1.44 (9H, s), 3.49 (2H, m), 4.51 (3H, m), 5.17 (2H, m), 5.79 (1H, br s), 7.20 -7.42 (8H, m). m/e (CI⁺) 497 (MH⁺).

d) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-amino-3-[N-(3,4-dichlorobenzyl)benzyloxycarbonylamino]propionamide

30 Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (762mg) was added to stirred solution of the product of step (c) (990mg),

1-methanesulfonylspro(3H indole-3,4'-piperidine) (580mg) and triethylamine (0.85ml) in dichloromethane (50ml). The resulting solution was stirred at room temperature for 18 hours, and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic layer was separated, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The recovered material was taken up in dichloromethane (20ml) and trifluoroacetic acid (2.0ml) was added. After 2 hours the solvent was evaporated under reduced pressure and the residue was partitioned between aqueous sodium carbonate (saturated, 20ml) and ethyl acetate (20ml). The organic layer was separated, dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a colourless foam (1.17g). m/e (CI⁺) 645 (MH⁺).

e) N-[1-Methanesulfonylspro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[N-(3,4-dichlorobenzyl)benzyloxycarbonylamino]propionamide

Benzaldehyde (171mg) was added to a solution of the product of step (d) (1.17g) in dichloromethane (50ml) stirring over MgSO₄. After 18 hours the solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (20ml) and treated with sodium borohydride (68mg). After 2 hours the solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC [CH₂Cl₂/MeOH/NH₃(Aq.), 96:3:1] to give the title compound as a colourless solid (410mg). m/e (CI⁺) 734 (MH⁺).

f) N-[1-Methanesulfonylspro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzylamino)propionamide, dihydrochloride

Boron tribromide (51.4mg) was added to a stirred solution of the product of step (e) (190mg) in dichloromethane at -5°C. After 20 minutes aqueous sodium hydroxide (4M) was added and the mixture was extracted with ethyl acetate (4x20ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC [CH₂Cl₂/MeOH/NH₃(Aq.), 96:3:1]. The residue was dissolved in ethanolic hydrogen chloride (5M) and the solvent was evaporated under reduced pressure. The residue was triturated with isopropanol and the solid was collected and dried *in vacuo* to give the title compound as a colourless solid (37 mg). NMR δ_H (250MHz, DMSO-d₆) 1.63-1.80 (4H, m), 2.09 (3H, m), 2.46 - 2.70 (3H, m), 2.84 (3H, s), 3.46-3.83 (5H, s) 4.56 (1H, m), 6.87-7.34 (12H, m). m/e (CI⁺) 601 (MH⁺).

EXAMPLE 73

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionamide, dihydrochloride

a) Methyl 2-(tert-butoxycarbonylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionate

Sodium cyanoborohydride (121mg) was added to a solution of formaldehyde (570mg), methyl 2-(tert-butoxycarbonylamino)-3-(3,4-dichlorobenzylamino)propionate (720mg) and acetic acid (0.1ml) in acetonitrile and the mixture was stirred at room temperature for 30 minutes. Aqueous sodium hydrogen carbonate (10ml) was added and the mixture was extracted with ethyl acetate (3x20ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a colourless oil (722mg). NMR δ_H (360MHz, CDCl₃) 1.45 (9H, s), 2.21 (3H, s), 2.73 (2H, d, J=7.0Hz), 3.46 (2H, m), 3.75 (3H, s) 4.37 (1H, m), 5.19 (1H, br s), 7.10 (1H, dd, J=11.0 and 1.0Hz), 7.36 (2H, m).

b) 2-(tert-Butoxycarbonylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionic acid

Lithium hydroxide (55mg) was added to a solution of the product of
5 step (a) (722mg) in tetrahydrofuran/water (30ml). The mixture was
stirred at room temperature for 4 hours, diluted with hydrochloric acid
(1M, 50ml) and extracted with ethyl acetate (3x50ml). The combined
organic fractions were dried (MgSO₄) and the solvent was evaporated
under reduced pressure to give the title compound as a colourless foam
10 (301mg). NMR δ_H (250MHz, CDCl₃) 1.43 (9H, s), 2.59 (3H, s), 2.90 (1H,
m), 3.22 (1H, m), 3.77 (1H, m) 4.10 (1H, m), 4.26 (1H, m), 5.67 (1H, br s)
7.24 (1H, dd, J=11.0 and 1.0Hz), 7.68 (2H, m). m/e (CI⁺) 377 (MH⁺).

c) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-amino-3-[N-methyl-3,4-dichlorobenzylamino]propionamide

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (305mg) was added to
stirred solution of the product of step (b) (301mg), N-1-
methanesulfonylspiro(3H-indole)-3,4'-piperidine (230mg) and
triethylamine (0.36ml) in dichloromethane (50ml). The mixture was
20 stirred at room temperature for 18 hours and the solvent was evaporated
under reduced pressure. The residue was partitioned between ethyl
acetate and water and the organic layer was dried (MgSO₄) and the
solvent was evaporated under reduced pressure. The residue was
dissolved in dichloromethane (20ml) and trifluoroacetic acid (2.0ml) was
25 added. After 2 hours the solvent was evaporated under reduced pressure
and the residue was partitioned between aqueous sodium carbonate
(saturated, 20ml) and ethyl acetate (20ml). The organic layer was dried
(MgSO₄) and the solvent was evaporated under reduced pressure to give
the title compound as a colourless foam. (380mg). m/e (CI⁺) 525 (MH⁺).

d) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionamide dihydrochloride

5 Benzaldehyde (80mg) was added to a solution of the product of step (c) (380mg) in dichloromethane (50ml) stirring over MgSO₄. After 18 hours the solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (20ml) and treated with sodium borohydride (29mg). After 2 hours the solvent was
10 evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC [CH₂Cl₂/MeOH/NH₃(Aq.), 96:3:1]. The residue was dissolved in ethanolic hydrogen chloride (5M) and the solvent was
15 evaporated under reduced pressure. The residue was triturated with isopropanol and the solid was collected and dried *in vacuo* to give the title compound as a colourless solid (220mg). NMR δ_H (360 MHz, DMSO-d₆) 1.60-2.09 (7H, m), 2.50 - 2.72 (3H, m), 2.91 (3H, s), 2.93 (3H, s) 3.46-3.83 (5H, 5) 4.47 (1H, m), 6.87-7.34 (12H, m). m/e (CI⁺) 615 (MH⁺).

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EXAMPLE 74

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-phenylpentanamide, hydrochloride

25 a) 2-[N-(Benzyl)benzyloxycarbonyl]amino-5-phenylpentanoic acid
 N-Benzyl-N-(benzyloxycarbonyl)serine- β -lactone [prepared according to Vederas, J. C., et. al., *J. Am. Chem. Soc.*, 109, 4649 (1987), 933mg, 3mmol] in THF (10ml) was added dropwise to a stirred, cooled (-78°C) solution of phenylethyl magnesium bromide dimethyl sulfide
30 complex [prepared from phenylethyl bromide (1.85g, 10mmol), magnesium (0.24g, 10mmol), copper (I) bromide dimethylsulfide complex (50mg) and

dimethylsulfide (0.5ml) in THF (20ml) (Vederas, J. C., et. al., *J. Am. Chem. Soc.*, **109**, 4649 (1987)]. The mixture was stirred at -78°C for 30 minutes then at -23°C for 2 hours. Aqueous hydrochloric acid (0.1M, 20ml) was added and the mixture was extracted with ethyl acetate (3x25ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/acetic acid (99.9:0.1) to give the title compound (253mg). NMR δ_H (250MHz, CDCl₃) 9.6-9.2 (1H, br s), 7.78-7.35 (15H, m), 5.53 (2H, s), 5.31-4.61 (3H, m), 2.78-2.62 (2H, m), and 2.47-1.63 (4H, m).

b) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-[N-(benzyl)benzyloxycarbonylamino-5-phenylpentanamide

The product of step (a) (250mg, 0.6mmol) was dissolved in dichloromethane (5ml) and 1-methanesulfonylspiro(3H-indole-3,4'-piperidine) hydrochloride (302mg, 1mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (254mg, 2mmol) and triethylamine (202mg, 2mmol) were added. The mixture was stirred at room temperature for 16 hours and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous potassium carbonate (saturated), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane to give the title compound (160 mg). m/e (CI⁺) 666 (MH⁺).

c) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-phenylpentanamide, hydrochloride

Boron tribromide (1M solution in dichloromethane, 1ml) was added to a stirred cooled (0°C) solution of the product of step (b) (150mg, 0.23mmol) in dichloromethane (1ml) and the mixture was stirred at 0°C for 30 minutes. Aqueous sodium hydroxide (2M) was added and the

organic layer was washed with water, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol and the residue was treated with methanolic hydrogen chloride. The solvent was evaporated under reduced pressure and the residue was freeze dried to give the title compound as an amorphous solid (165mg). Found: C, 65.78; H, 6.94; N, 7.65. C₃₁H₃₇N₃O₃S.HCl requires: C, 65.53; H, 6.75; N, 7.40%. m/e (CI⁺) 532 (MH⁺).

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EXAMPLE 75

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)pentanamide, hydrochloride

a) Ethyl 5-(3,4-dichlorophenyl)-2-oxopentanoate

3-(3,4-Dichlorophenyl)propylmagnesium bromide [prepared from 3-(3,4-dichlorophenyl)propyl bromide (2.7g, 10mmol) and magnesium (0.24g, 10mmol) in ether (*Ger. Offen.* DE1965711)] was added dropwise to a stirred, cooled (-10°C) solution of diethyl oxalate (1.75g, 4.2mmol) in ether (60ml). THF (15ml) was added and the mixture was stirred at room temperature for 0.5 hours. Hydrochloric acid (2M) was added and the organic layer was diluted with hexane, washed with brine and aqueous sodium hydrogen carbonate (saturated), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (25:75) to give the title compound as an oil (0.7 g). NMR δ_H (360MHz, CDCl₃) 7.35 (1H, d, J=6.4Hz), 7.28 (1H, d, J=2Hz), 7.01 (1H, dd, J=6.4, 2Hz), 4.39-4.25 (2H, m), 2.84 (2H, t, J=7.2Hz), 2.62 (2H, t, J=7.2Hz), 2.09-1.91 (2H, pent, J=8Hz), and 1.33 (3H, t, J=7Hz).

30

b) Ethyl 2-(Benzylamino)-5-(3,4-dichlorophenyl)pentanoate

Acetic acid (0.42g, 7mmol) was added to a mixture of the product of step (a) (1.0g, 3.5mmol), benzylamine (0.75g, 7mmol) and sodium cyanoborohydride (440mg, 7mmol) in ethanol (10ml) and the mixture was stirred at room temperature for 72 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and aqueous potassium carbonate (saturated). The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (5:95) to give the title compound (400mg). NMR δ_H (360MHz, CDCl₃) 7.32-7.23 (7H, m), 6.96 (1H, dd, J=8.4, 2.2Hz), 4.18 (2H, q, J=7Hz), 3.81 (1H, d, J=12.9Hz), 3.61 (1H, d, J=12.9Hz), 3.23 (1H, t, J=7.2Hz), 2.54 (2H, m), 1.69-1.60 (4H, m), and 1.28 (3H, t, J=7Hz).

15 c) Ethyl 2-[N-(benzyl)-*tert*-butyloxycarbonylamino]-5-(3,4-dichlorophenyl)pentanoate

Di-*tert*-butyldicarbonate (400mg) was added to the product of step (b) (400mg) in dichloromethane (10ml) and the mixture was stirred at room temperature for 72 hours. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (100:0 increasing to 95:5) to give the title compound (350mg). NMR δ_H (360MHz, CDCl₃) 7.29-7.11 (6H, m), 7.12-7.11 (1H, m), 6.87-6.85 (1H, m), 4.11-3.88 (5H, m), 2.44-1.29 (6H, m), 1.42 (9H, s), and 1.20 (3H, t, J=7Hz).

25

d) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)pentanamide, hydrochloride

A solution of lithium hydroxide (100mg) in water (10ml) was added to a solution of the product of step (c) (350mg) in THF (10ml) and the mixture was stirred at room temperature for 16 hours. The mixture was acidified with aqueous citric acid (10%) and extracted with ethyl acetate

30

(3x25ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (5ml) and 1-methanesulfonylspiro(3H-indole-3,4'-piperidine) hydrochloride (215mg, 0.71mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (199mg, 0.78mmol) and triethylamine (202mg, 2mmol) were added. The mixture was stirred at room temperature for 16 hours and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous potassium carbonate (saturated), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane and the residue was dissolved in ethanolic hydrogen chloride (5M). The solvent was evaporated under reduced pressure and the residue was freeze dried to give the title compound as an amorphous solid (235mg). Found: C, 58.66; H, 5.70; N, 6.60. C₃₁H₃₅Cl₂N₃O₃S.HCl requires: C, 58.45; H, 5.70; N, 6.60%. m/e (Cl⁺) 600 (MH⁺).

EXAMPLE 76

N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)butanamide, hydrochloride

a) Ethyl 4-(3,4-Dichlorophenyl)-2-oxobutanoate
2-(3,4-Dichlorophenyl)ethyl bromide (5g, 19.7mmol) was added slowly to a suspension of magnesium turnings (0.48g, 19.7mmol) in ether (30ml). After spontaneous reflux had finished the mixture was stirred under reflux for 15 minutes and allowed to cool to room temperature. The mixture was added dropwise via cannula to a stirred, cooled (-25°C) solution of diethyl oxalate (3g, 20.7mmol) in THF (15ml). The mixture was stirred at -10°C for 30 minutes and allowed to warm to room temperature. Hydrochloric acid (2M, 15ml) was added and the mixture was extracted with ether (2x20ml). The combined organic fractions were

washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (10:90) to give the title compound (0.7 g).

5

b) Ethyl 2-(benzylamino)-4-(3,4-dichlorophenyl)butanoate

A mixture of acetic acid (0.29ml, 5mmol), the product of step (a) (700mg, 2.5mmol), benzylamine (0.56ml, 5mmol) and sodium cyanoborohydride (320mg, 5mmol) in ethanol (10ml) was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and aqueous sodium carbonate (saturated). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (10:90) to give the title compound as an oil (310 mg). m/e (CI^+) 366 (MH^+).

c) Ethyl 2-[N-(benzyl)-tert-butyloxycarbonylamino]-4-(3,4-dichlorophenyl)butanoate

Di-tert-butylidicarbonate (900mg, 4.1mmol) was added to the product of step (b) (300mg, 0.82mmol) in dichloromethane (10ml) and the mixture was stirred at room temperature for 5 days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (90:10) to give the title compound as an oil (281 mg). m/e (CI^+) 466 (MH^+).

d) 2-[N-(Benzyl)-tert-butyloxycarbonylamino]-4-(3,4-dichlorophenyl)butanoic acid

Lithium hydroxide (80mg 1.8mmol) and water (2 ml) were added to a solution of the product of step (c) (280mg, 0.6mmol) in THF (5ml) and the mixture was stirred at room temperature for 16 hours. Acetic acid

(0.5ml) was added and the mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound as a colourless foam (234mg). m/e (CI^+) 438 (MH^+).

5

e) N-[1-Methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-4-(3,4-dichlorophenyl)butanamide, hydrochloride

A mixture of the product of step (e) (230mg, 0.53mmol), 1-methanesulfonylspiro(3H-indole-3,4'-piperidine) hydrochloride (159mg, 0.53mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (160mg, 0.64mmol) and triethylamine (0.18ml, 1.33mmol) in dichloromethane (10ml) was stirred at room temperature for 16 hours. Dichloromethane (10ml) was added and the mixture was washed with aqueous sodium carbonate (saturated) and aqueous citric acid (10%), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/hexane (70:30). The residue was dissolved in methanol (2ml) and methanolic hydrogen chloride (5ml) was added. The mixture was stirred at room temperature for 16 hours and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (2ml) and ether was added. The solid was collected and dried *in vacuo* to give the title compound as a colourless solid (235mg). Found: C, 57.36; H, 5.53; N, 6.71. $\text{C}_{30}\text{H}_{33}\text{Cl}_2\text{N}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 0.25\text{H}_2\text{O}$ requires: C, 57.42; H, 5.54; N, 6.70%. m/e (CI^+) 586 (MH^+).

25

and R^b are as previously defined; heteroaryl selected from indazolyl, thienyl, furanyl, pyridyl, thiazolyl, tetrazolyl and quinolinyl; naphthyl; benzhydryl; or benzyl; wherein each heteroaryl, the naphthyl group and each phenyl moiety of benzyl and benzhydryl may be substituted by

5 C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl;

R³ and R⁴ each independently represents hydrogen or C₁₋₆alkyl or R³ and R⁴ together are linked so as to form a C₁₋₃alkylene chain;

R⁵ represents hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenylC₁₋₄alkyl, CO₂R^a, CONR^aR^b, SOR^a or SO₂R^a,
10 wherein the phenyl moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl, and R^a and R^b are as previously defined;

X and Y each independently represents hydrogen, or together form a group =O; and

Z represents a bond, O, S, SO, SO₂, NR⁶, or -(CR⁶R⁶)- where each R⁶
15 is hydrogen or C₁₋₆alkyl;
or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein
n is zero, 1, 2 or 3;

20 R represents C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, halogen, cyano, trifluoromethyl, SO₂C₁₋₆alkyl, NR^aR^b, NR^aCOR^b, or CONR^aR^b, where R^a and R^b each independently represent hydrogen, C₁₋₆alkyl, phenyl or trifluoromethyl;

R¹ represents phenyl optionally substituted by 1, 2 or 3 groups
25 selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, -O(CH₂)_pO- where p is 1 or 2, halogen, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b, where R^a and R^b are as previously defined;

30 R² represents phenyl optionally substituted by 1, 2 or 3 groups selected from C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl,

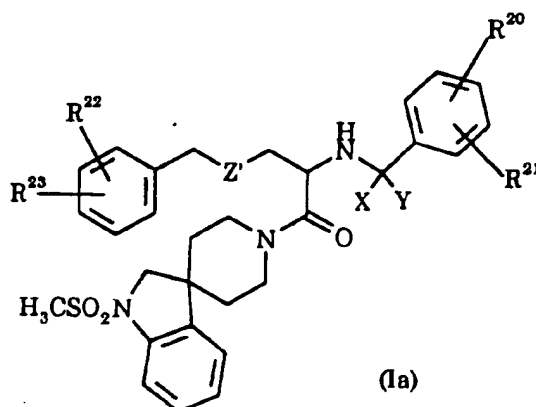
C₃₋₇cycloalkyl, C₁₋₄alkyl, -O(CH₂)_pO- where p is 1 or 2, halogen, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a, SR^a, SOR^a, SO₂R^a, NR^aR^b, NR^aCOR^b, NR^aCO₂R^b, COR^a, CO₂R^a or CONR^aR^b, where R^a and R^b are as previously defined; heteroaryl selected from indazolyl, thienyl, furanyl, pyridyl, thiazolyl, tetrazolyl and quinoliny; naphthyl; benzhydryl; or benzyl; wherein each heteroaryl, the naphthyl group and each phenyl moiety of benzyl and benzhydryl may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl;

10 R³ and R⁴ each independently represents hydrogen or C₁₋₆alkyl;
R⁵ represents hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, phenylC₁₋₆alkyl, CO₂R^a, CONR^aR^b, SO₂R^a or SO₂R^a, wherein the phenyl moiety may be substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halogen or trifluoromethyl, and R^a and R^b are as previously defined;

15 X and Y each independently represents hydrogen, or together form a group =O; and

Z represents O, S, or NR⁶, where R⁶ is hydrogen or C₁₋₆alkyl; or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 1 of the formula (Ia):



wherein

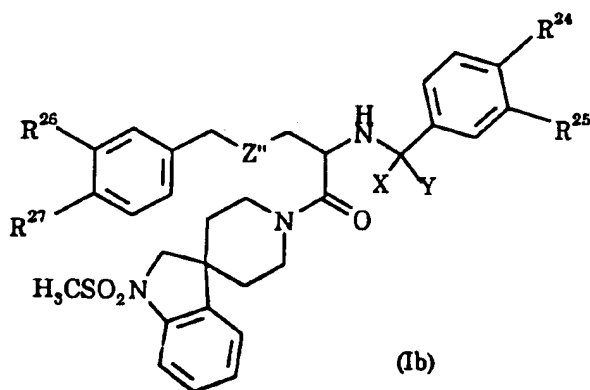
X and Y are as defined in claim 1:

Z' is O, S or -CH₂-;

R²⁰ and R²¹ independently represent hydrogen, C₁₋₈alkyl, halogen, trifluoromethyl, OR^a, or NR^aR^b, where R^a and R^b are as defined in claim 1; and

**R²² and R²³ independently represent hydrogen or halogen;
5 or a pharmaceutically acceptable salt thereof.**

4. A compound as claimed in claim 1 of the formula (Ib):



10

wherein

Z'' is O or -CH₂-;

R²⁴ and R²⁵ independently represent hydrogen or chlorine; and

R²⁶ and R²⁷ independently represent hydrogen or chlorine, with the proviso that at least one of R²⁶ and R²⁷ represents chlorine; or a pharmaceutically acceptable salt thereof.

5. A compound as claimed in claim 1 wherein n is zero.

20 6. A compound as claimed in claim 1 wherein R¹ represents unsubstituted phenyl or phenyl substituted by one or two groups selected from C₁₋₆alkyl, halogen and trifluoromethyl.

7. A claim as claimed in claim 6 wherein R¹ represents disubstituted phenyl.

5 8. A compound as claimed in claim 1 wherein R² represents unsubstituted or substituted phenyl, thienyl, furanyl, pyridyl, quinolinyl, naphthyl, or benzhydryl.

9. A compound as claimed in claim 8 wherein R² represents unsubstituted phenyl or phenyl substituted by one or two groups selected
10 from chlorine, fluorine, methyl, trifluoromethyl, methoxy and dimethylamino.

10. A compound as claimed in claim 1 wherein R³ and R⁴ each independently represent hydrogen.

15

11. A compound as claimed in claim 1 wherein R⁵ represents the group SO₂R^{*} where R^{*} is as defined in claim 1.

12. A compound as claimed in claim 11 wherein R⁵ represents
20 SO₂CH₃.

13. A compound as claimed in claim 1 wherein Z is an oxygen atom.

25 14. A compound as claimed in claim 1 wherein Z is -CH₂-.

15. A compound selected from:
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-
2-(3,4-dichlorobenzamido)propionamide;
30 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-
2-(3-pyridylcarboxamido)propionamide;

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzamido)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-chlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzamido)propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,5-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzamido)propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-benzamidopropionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-(2-propyloxy)benzamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(1-naphthyl)carboxamido]propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(2-naphthyl)carboxamido]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(phenylacetamido)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorophenylacetamido)propionamide;
- 30

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(3,5-bis(trifluoromethyl)phenyl)acetamido]propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(diphenylacetamido)propionamide;
5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylcarboxamido)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylcarboxamido)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(8-quinolinylcarboxamido)propionamide;
10 or a pharmaceutically acceptable salt thereof.

16. A compound selected from:

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dichlorobenzylamino)propionamide;
15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-methoxybenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-benzyloxypropionamide;
20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-chlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-25 2-(4-chlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-bromobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-fluorobenzylamino)propionamide;
30 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-cyanobenzylamino)propionamide;

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-nitrobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methylbenzylamino)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-methoxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-methoxybenzylamino)propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-(dimethylamino)benzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,4-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dichlorobenzylamino)propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,3-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2,6-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,5-dimethoxybenzylamino)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-chloro-5-methoxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-dimethoxybenzylamino)propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3,4-methylenedioxybenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(1-naphthylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-naphthylmethylamino)propionamide;
- 30

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-pyridylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(3-pyridylmethylamino)propionamide;
- 5 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(4-pyridylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(2-furylmethylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(5-methylfur-2-yl)methylamino]propionamide;
- 10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(3-methylthiophen-2-yl)methylamino]propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-[(5-methylthiophen-2-yl)methylamino]propionamide;
- 15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-benzyloxy-2-(N-(3,4-dichlorobenzyl)-N-(methyl)amino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(2-chlorobenzyloxy)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(3-chlorobenzyloxy)propionamide;
- 20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(4-chlorobenzyloxy)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(2-chlorobenzyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
- 25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3-chlorobenzyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(4-chlorobenzyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(benzylthio)-2-(3,4-dichlorobenzylamino)propionamide;
- 30

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-benzylamino-3-(3,4-dichlorobenzyloxy)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzyloxy)-2-(3,4-dichlorobenzylamino)propionamide;
5 or a pharmaceutically acceptable salt thereof.

17. A compound selected from:

- N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naph-2-yl)methoxy]propionamide;
10 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-[(naph-1-yl)methoxy]propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-[N-(methyl)benzylamino]-3-(3,4-dichlorobenzyloxy)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzyloxy)-2-(dimethyl)aminopropionamide;
15 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylthio)-2-(benzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-3-(3,4-dichlorobenzylsulfonyl)-2-(benzylamino)propionamide;
20 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2,3-bis(benzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(3,4-dichlorobenzylamino)propionamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-3-(N-methyl-3,4-dichlorobenzylamino)propionamide;
25 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-phenylpentanamide;
N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)pentanamide;
30 N-[1-methanesulphonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(benzylamino)-5-(3,4-dichlorophenyl)butanamide;

or a pharmaceutically acceptable salt thereof.

18. A compound selected from:

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-

5 (benzylamino)-3-(3,4-dichlorobenzyloxy)propionamide;

N-[1-methanesulfonylspiro(3H-indole-3,4'-piperidin)-1-yl]-2-(3,4-dichlorobenzylamino)-3-(3,4-dichlorobenzyloxy)propionamide;

or a pharmaceutically acceptable salt thereof.

10 19. A compound as claimed in any preceding claim for use in therapy.

20. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 18 in association with a
15 pharmaceutically acceptable carrier or excipient.

21. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin
20 reducing amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

25 22. A method according to claim 21 for the treatment or prevention of pain or inflammation.

23. A method according to claim 21 for the treatment or prevention of migraine.

30

24. A method according to claim 21 for the treatment or prevention of emesis.

5 25. A method according to claim 21 for the treatment or prevention of postherpetic neuralgia.

10 26. The use of a compound as claimed in any one of claims 1 to 18 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

27. The use of a compound as claimed in any one of claims 1 to 18 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

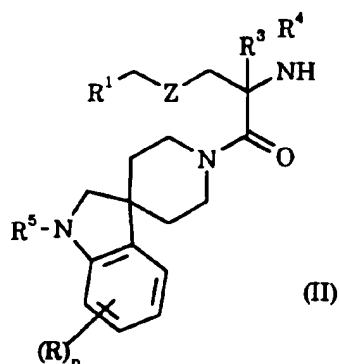
15 28. The use of a compound as claimed in any one of claims 1 to 18 for the manufacture of a medicament for the treatment or prevention of migraine.

20 29. The use of a compound as claimed in any one of claims 1 to 18 for the manufacture of a medicament for the treatment or prevention of emesis.

25 30. The use of a compound as claimed in any one of claims 1 to 18 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.

31. A process for the preparation of a compound of formula (I) as claimed in claim 1, which comprises:

30 (A), where X and Y are both hydrogen, reacting a compound of formula (II):



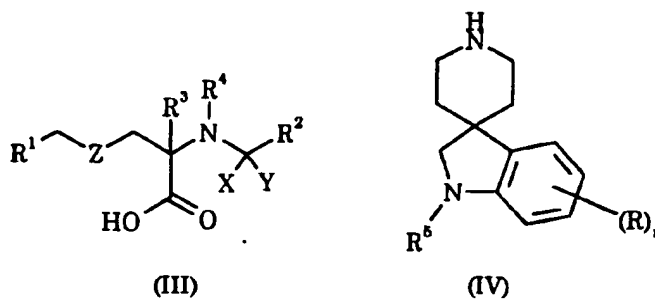
wherein R, R¹, R³, R⁴, R⁵, Z and n are as defined in claim 1, with an aldehyde of formula R²-CHO in the presence of a reducing agent; or

5

(B), where X and Y together form a group =O, may be prepared by the reaction of a compound of formula (II) with an acyl halide of formula R²-COHal where Hal is a halogen atom; or

10

(C) by the reaction of a compound of formula (III) with a piperidinyll derivative of formula (IV):



15

wherein R, R¹, R², R³, R⁴, R⁵, X, Y, Z and n are as defined in claim 1 with the proviso that R⁵ is not hydrogen;

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

5 and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/GB 95/01867

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/10 A61K31/435 //(C07D471/10,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 360 390 (GLAXO) 28 March 1990 see claims 1,12 ---	1,20
A,P	WO,A,94 29309 (MERCK) 22 December 1994 see page 46, line 9 - line 15; claim 1 -----	1,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

20 October 1995

Date of mailing of the international search report

27. 10. 95

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/01867

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21-25 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/01867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-360390	28-03-90	JP-A- 2124887 US-A- 5166136	14-05-90 24-11-92
WO-A-9429309	22-12-94	AU-B- 7201194	03-01-95